UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/007,047	12/06/2001	Theodora Ross	UM-06692	6232

7590 10/18/2006

Tanya A. Arenson
MELDEN & CARROLL, LLP
Suite 350
101 Howard Street
San Francisco, CA 94105

EXAMINER	
FETTEROLF, BRANDON J	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 10/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/007,047	ROSS ET AL.	
	Examiner	Art Unit	
	Brandon J. Fetterolf, PhD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 August 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-27,29,36,84-86,91-93 and 95* is/are pending in the application.

4a) Of the above claim(s) *84-86 and 91-93* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-27, 29, 36 and 95* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Response to Amendment

The Amendment filed on 08/07/2006 in response to the previous Non-Final Office Action (05/05/2006) is acknowledged and has been entered.

Claims 24-27, 29, 36, 84-86, 91-93 and 95 are currently pending.

Claims 84-86 and 91-93 are withdrawn from consideration as being drawn to a non-elected invention.

Claims 24-27, 29, 36 and 95 are currently under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

New Rejections necessitated by amendment:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 24-27, 29, 36 and 95 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of characterizing prostate cancer in a patient already diagnosed with prostate cancer by detecting the presence or absence of HIP1 in a sample with a nucleic acid probe configured to hybridize to a HIP1 nucleic acid sequence consisting of the nucleic acid sequence of SEQ ID NO: 1, wherein the absence of HIP1 in said sample is indicative of PSA non-recurrence and/or recurrence free survival, does not reasonably provide enablement for a method of characterizing prostate cancer in a patient already diagnosed with prostate cancer by detecting the presence or absence of HIP1 in a sample with a nucleic acid probe configured to hybridize to a HIP1 nucleic acid sequence consisting of the nucleic acid sequence of SEQ ID NO: 1, wherein the absence or presence of HIP1 is indicative the stage of said cancer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the nature of the invention, (2) the relative skill of those in the art, (3) the breadth of the claims, (4) the amount or direction or guidance presented, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the state of the prior art, and (8) the predictability or unpredictability of the art.

Although the quantity of experimentation alone is not dispositive in a determination of whether the required experimentation is undue, this factor does play a central role. For example, a very limited quantity of experimentation may be undue in a fledgling art that is unpredictable where no guidance or working examples are provided in the specification and prior art, whereas the same amount of experimentation may not be undue when viewed in light of some guidance or a working example or the experimentation required is in a predictable established art. Conversely, a large quantity of experimentation would require a correspondingly greater quantum of guidance, predictability and skill in the art to overcome classification as undue experimentation. In Wands, the determination that undue experimentation was not required to make the claimed invention was based primarily on the nature of the art, and the probability that the required experimentation would result in successfully obtaining the claimed invention. (Wands, 8 USPQ2d 1406) Thus, a combination of factors which, when viewed together, would provide an artisan of ordinary skill in the art with an expectation of successfully obtaining the claimed invention with additional experimentation would preclude the classification of that experimentation as undue. A combination of Wands factors, which provide a very low likelihood of successfully obtaining the claimed invention with additional experimentation, however, would render the additional experimentation undue.

The nature of the invention

The claims are drawn to a method of characterizing prostate cancer in a subject diagnosed with prostate cancer comprising detecting the presence or absence of HIP1 with a nucleic acid probe configured to hybridize to a HIP1 nucleic acid sequence consisting of the nucleic acid sequence of SEQ ID NO: 1. The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Level of skill in the art

The level of skill in the art is deemed to be high, generally that of a PhD or MD.

The breadth of the claims

Applicants broadly claim, in part, a method of characterizing prostate cancer in a patient already diagnosed with prostate cancer by detecting the presence or absence of HIP1 in a sample with a nucleic acid probe configured to hybridize to a HIP1 nucleic acid sequence consisting of the nucleic acid sequence of SEQ ID NO: 1, wherein the absence or presence of HIP1 is indicative the stage of said cancer. The claims are further drawn to said "stage" of cancer is selected from the group consisting of high-grade prostatic intraepithelial neoplasia, benign prostatic hyperplasia, prostate carcinoma and metastatic prostate carcinoma.

Guidance in the specification and Working Examples

The specification teaches (page 4, lines 9-12) that HIP1 may be utilized in a method for characterizing prostate tissue in a subject, wherein the presence or absence of HIP1 characterizes the tissue sample. For example, the specification teaches that HIP1 expression in individual patients reveals that there were progressively higher frequencies of HIP1 expression in benign, PIN, PCA and metastatic case. Conversely, there were progressively lower frequencies of the lack of HIP1 expression among the same (page 65, lines 25-28 and Figure 4a). Moreover, the specification teaches the clinical implications associated with HIP1 expression, wherein patients with tumors which did not stain for HIP1 expression did not develop a PSA recurrence (page 66, lines 5-11 and page 67, Table 1). In addition, the specification teaches that there is a survival advantage of PCa

patients with tumors that had no HIP1 expression, wherein all patients that lacked HIP1 expression survived 67 months without evidence of recurrence as compared to 28% of the patients whose tumors expressed HIP1 died of prostate cancer (page 66, lines 17-26 and Figure 4b). Thus, while the specification teaches that in some instances there is a correlation between HIP1 expression and prostate cancer, the specification does not appear to provide a nexus between the presence or absence of HIP1 in prostate tissues and the patients risk of prostate specific antigen failure, the risk of prostate cancer metastasizing, the risk of prostate cancer reoccurring or assessing the state of prostate cancer. For example, while the specification (page 65, lines 28-31) teaches the presence of HIP1 expression correlated with the ordinal categories of benign vs. PIN vs. PCa vs. Metastatic, the specification appears to be silent on an "amount" of HIP1 which can be used to differentiate the stage of cancer because the results shown in Figure 4a shows the frequency (% cases) of HIP1 expression and not a differentiating amount.

Quantity of experimentation

The quantity of experimentation in the areas of cancer diagnosis and/or characterizing a particular stage of cancer is extremely large given that what may be "preferable" in the lab is only suggestive and does not qualify as a reasonable expectation of success, especially in a highly unpredictable art such as determining the a particular stage of cancer.

The unpredictability of the art and the state of the prior art

The state of the art at the time of filing was such that one of skill could recognize that the expression of a cancer-associated nucleic acid molecule that appears to be 60% identical to the instantly claimed nucleic acid of SEQ ID NO: 1 has been found to be associated with colon cancer (see Chen et al. US 6,794,501, of record). With regards to HIP1 and/or a nucleic acid sequence consisting of SEQ ID NO: 1, the prior art appears to be silent an association of HIP1 and/or a nucleic acid consisting of SEQ ID NO: 1 and prostate cancer, and further, HIP1 being an identifier of a particular stage of prostate cancer.

It is noted, as stated above, that the specification (page 65, lines 28-31) teaches the presence of HIP1 expression correlated with the ordinal categories of benign vs. PIN vs. PCa vs. Metastatic. However, the specification appears to be silent on an "amount" of HIP1 which can be used to

differentiate the stage of cancer because the results shown in Figure 4a shows the frequency (% cases) of HIP1 expression and not a differentiating amount. Therefore, the teachings above do not clearly indicate whether or not HIP1 is indicative of the cancerous state in prostate cells. In other words, what may be "preferable" in the lab is only suggestive and does not qualify as a reasonable expectation of success, especially in a highly unpredictable art such as determining the stage of prostate cancer. For example, Tockman *et al* (Cancer Res., 1992, 52:2711s-2718s, *of record*) teach considerations necessary in bringing a cancer biomarker (intermediate end point marker) to successful clinical application. Although, the reference is drawn to biomarkers for early lung cancer detection, the basic principles taught are clearly applicable to other oncogenic disorders such as prostate cancer. Tockman *et al* teaches that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials (see abstract). Early stage markers of carcinogenesis have clear biological plausibility as markers of preclinical cancer and **if validated** (emphasis added) can be used for population screening (p. 2713s, col. 1). The reference further teaches that once selected, the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed) cancer outcome. The essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of clinical cancer and *link* those marker results with subsequent histological confirmation of disease. This irrefutable link between antecedent marker and subsequent acknowledged disease is the essence of a valid intermediate end point marker (p. 2714, see Biomarker Validation against Acknowledged Disease End Points). Clearly, prior to the successful application of newly described markers, markers must be validated against acknowledged disease end points and the marker predictive value must be confirmed in prospective population trials (p. 2716s, col 2). In addition, Slamon et al. (Science Vol. 235, January 1987, pages 177-182, *of record*) teach other essential factors that are known to be important in the prognosis of breast cancer in individual patients such as size of the primary tumor, stage of the disease at diagnosis, hormonal receptor status, and number of axillary lymph nodes involved with disease (page 178, 1st column, 2nd paragraph). Such data are critical to assessing actuarial curves for relapse (Figure 3), and for comparing disease-free survival and overall survival to prognostic factors (Table 4).

Conclusion

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the lack of guidance provided in the specification for correlation in vitro results to in vivo success, and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as written.

In response to the previous rejection of claims 24-27, 29, 36 and 95 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, Applicants have amended the claims to recite "...wherein the presence of absence of HIP1 in said sample is indicative of one or more properties of said cancer selected from the group consisting of PSA reoccurrence, recurrence free survival, and stage of said cancer (underline = amended). As such, the instant "scope" rejection reflects the amended claims, wherein the specification is being enabling for a method of characterizing prostate cancer in a patient already diagnosed with prostate cancer by detecting the presence or absence of HIP1 in a sample with a nucleic acid probe configured to hybridize to a HIP1 nucleic acid sequence consisting of the nucleic acid sequence of SEQ ID NO: 1, wherein the absence of HIP1 in said sample is indicative of PSA non-recurrence and/or recurrence free survival. However, the specification does not reasonably provide enablement for a method of characterizing prostate cancer in a patient already diagnosed with prostate cancer by detecting the presence or absence of HIP1 in a sample with a nucleic acid probe configured to hybridize to a HIP1 nucleic acid sequence consisting of the nucleic acid sequence of SEQ ID NO: 1, wherein the absence or presence of HIP1 is indicative the stage of said cancer for the reasons set forth above. Therefore, the "stage of cancer" part of the previous rejection is maintained. In response to this "part" of the previous rejection, Applicants submit that as stated by the Examiner, the specification teaches "HIP1 expression in individual patients reveals that there were progressively higher frequencies of HIP1 expression in benign, PCA and metastatic case." (Office Action, pages 3-4). In response to this argument, the Examiner concedes that the previous statement is correct. However, as stated in the previous office action, as well as above, the specification appears to be silent on an "amount" of HIP1 which can be used to differentiate the stage of cancer because the results shown in Figure 4a shows the frequency (% cases) of HIP1 expression and not a differentiating amount. As a result, it

is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as written.

Therefore, No claim is allowed.

Conclusion

The closest prior art to the instantly claimed invention is Chen et al. (US 6,794,501, of record) whom teaches a method of diagnosing colon cancer is a subject comprising obtaining a biological sample from a subject and determining the expression of a cancer-associated nucleic acid molecule that appears to be 60% identical to the instantly claimed nucleic acid of SEQ ID NO: 1. However, Chen et al. do not teach or suggest that the nucleic acid can be used to determine the of risk of prostate specific antigen failure, risk of cancer metastasizing, risk of cancer reoccurring, and stage of cancer.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeff Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Brandon J Fetterolf, PhD
Patent Examiner
Art Unit 1642

JEFFREY SIEW
SUPERVISORY PATENT EXAM

BF